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SMOKING AND HEALTH: THE UNRESOLVED DEBATE

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PREFACE

A great deal of publicity is given to the alleged association between smoking and certain diseases and to the views of those doctors and scientists who believe that smoking has been proven to be a cause of disease. Less attention, however, is paid to other medical and scientific research which challenges this view, and which casts doubt upon such a simple causal hypothesis. The purpose of the enclosed document is to try to redress this balance by pointing out many of the inconsistencies and anomalies that now exist. The document is not intended to provide a comprehensive review of all smoking and health research and it neither seeks to nor can it reach any conclusions. What it does demonstrate is that many of the findings do not support the simple causal theory, and it highlights the need for further research.

The document in fact represents a summary of a collection of epidemiological studies representing anomalies in the evidence usually used to suggest that smoking is associated with various diseases.

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7 SUMMARY AND CONCLUSION

This document provides "the other side" to the smoking and health controversy by means of the following arguments:

1 A general criticism of the science of epidemiology, the data (e.g. death certificates) on which studies are based, and the uses that can be made of epidemiological results (particularly in terms of causality).

2 A detailed discussion of the association between smoking and lung cancer, pointing out anomalies in the following areas:

- lack of consistency in the size of the relative risks obtained in the range of prospective studies on smoking and lung cancer carried out up until 1970;

- anomalies in the dose-response relationship for the association between smoking and lung cancer;

- differences in the incidence of lung cancer (independent of smoking habits) in different geographical and ethnic groups;

- increasing rates of a type of lung cancer not usually claimed to be associated with cigarette smoking, relative to decreases, or no change in, so-called smoking-associated forms of lung cancer.

- evidence suggesting that, in many countries lung cancer and other smoking-associated diseases have been declining for some time in younger generations, particularly in men, but also in women.

3 A discussion of the many other factors that are claimed to be associated with lung cancer. These include: radon, diesel exhaust, many different occupational exposures, environmental pollution, diet, familial and genetic factors, alcohol and other drugs, stress and personality factors.

4 Similar arguments are provided, in less detail and where available, for other smoking-associated diseases:

(a) Other cancers

- data suggest that death rates from oesophageal and laryngeal cancer are falling, and do not correlate positively with rates of cigarette smoking.

- other factors are discussed that are believed to be associated with the cancers that have also been associated with smoking e.g. alcohol for oral, oesophageal and laryngeal cancers; occupation and artificial sweetners for bladder cancer; sexual behaviour and viruses for cervical cancer.

(b) Heart disease

- the paucity of evidence associating smoking with some forms of heart disease is noted.

- the importance is also noted of around 245 other factors that have been suggested to constitute risk factors for heart disease, particularly diet, cholesterol, weight, and environmental factors.

- there are indications that heart disease is declining in many countries, particularly in younger generations.

(c) Chronic obstructive lung disease

- the existence is noted of many factors other than smoking that have been associated with COLD e.g. respiratory illness in childhood, social class, occupation, genetic components, environment.

- evidence exists that COLD has been declining rapidly in some countries e.g. the UK, for some years.

5 Three factors that are believed to be extremely important in disease in general, geographical/ethnic factors, diet, and genetic factors are considered in more detail.

One can conclude from this evidence that, although many studies have claimed to find associations between smoking and certain diseases, further research is clearly necessary to investigate the basis of this claimed association. A simple causal model is not consistent with the above evidence.

2 INTRODUCTION

Smoking and health is not a new subject, nor even one restricted to the present century. In earlier centuries there were several celebrated outcries against tobacco, and its use has sometimes been proscribed by severe penalties. But it was not until this century that suggestions first arose of a possible association between smoking and the incidence of certain diseases (e.g. Adler 1912). Subsequently numerous studies have been published claiming a statistical relationship (association) between smoking and a variety of diseases. Many doctors have interpreted these studies as indications that smoking actually causes diseases such as lung cancer.

It is, however, a well-known scientific principle that one should not (without further supporting evidence) assume that, because two factors are statistically associated, one caused the other.

The validity of judgements on smoking and disease has therefore been repeatedly challenged. Eminent scientists such as the late Sir Ronald Fisher (1959) have warned against the uncritical acceptance of the view that smoking must be the cause of diseases with which it is said to be statistically associated. Attention has also been drawn to inconsistencies in the basic statistical data and to the lack of understanding of the fundamental mechanisms of disease. Such warnings have been repeated more recently by Hickey and Allen (1983), Hickey (1987) and Morowitz (1975). It is also recognised that interpretation of statistical evidence involves personal judgements. A publication by the Open University on "Smoking, Statistics and Society" states:

> "In lung cancer research, different researchers have made different choices: some have done experiments on many different kinds of animal; some have carried out observational studies on humans; and some have worked on single cells from human or animal tissues. The results of all these studies, taken together, provide for most people overwhelming evidence of a causal relationship between smoking and lung cancer. Nevertheless, whether or not this evidence is overwhelming remains a matter of personal judgement."

Over the last 20-30 years members of the medical communities in many countries have judged that a causal relationship does exist. This tenet has also been widely accepted by governments and the public, and for this reason legislation and ordinances affecting smoking are commonplace.

In the period since the original judgements were made, however, there have been many developments in relevant fields of statistics and science. Modern computers enable complex statistical analyses of data from large population studies (epidemiology) to examine possible associations between diseases and many different factors. Details of the chemical structure of cells (molecular biology) are being elucidated; this may lead to a better understanding of the processes leading to certain diseases. Emphysema, for instance, is now known to be related to a genetic abnormality in some people.

Scientists are beginning to develop models to explain how certain diseases may develop. For example, Burch (1976) has published a complete model for the development of many diseases. He believes that genetic material in cells is inherently unstable and subject to spontaneous changes which may result in disease. Other authors have also proposed models for some types of cancer, using their knowledge of the way in which viruses and chemicals can affect the essential functions of cells in the body.

It is the purpose of this document to list some of the recent research which might be considered 'anomalous' in the sense that the reported results do not sit comfortably with the causal model of the relationship between smoking and certain diseases.

'Anomalies' are, of course, a reflection of human ignorance since it should be theoretically possible to produce a model which accommodates all known facts. In the case of smoking, however, the complexity of the problem and its intellectual challenge are formidable obstacles to rapid progress.

On the subject of anomalies in scientific areas, it is perhaps worth considering the views of the influential philospher of science, Karl Popper. Popper (1974) noted that it is always possible to evade evidence that would otherwise falsify a theory and that it is always possible, by one means or another, to achieve agreement between a theory and observational evidence. If certain evidence is inconsistent with the theory, a number of strategies are often pursued to "save" it. The conflicting evidence may be rejected outright, or it may be accounted for by adding auxiliary hypotheses, thus introducing a staggering degree of complexity into a theoretical system.

According to Popper, proper scientific method is continually to expose a theory to the possibility of being falsified. He proposed a set of methodological rules for the empirical sciences. The supreme rule is a criterion of adequacy for all other rules, stating that the rules of empirical method

> "must be designed in such a way that they do not protect any statement in science against falsification."

Popper viewed the history of science as a sequence of conjectures, refutations, revised conjectures and additional refutations. He concluded that the distinguishing characteristic of scientific interpretations is their "susceptibility to revision." According to Popper, to insist that scientific interpretations continually be exposed to the possibility of falsification is to promote scientific progress. In the interpretation of smoking and health research, these concepts are frequently not applied.

3. EPIDEMIOLOGICAL METHODS

Epidemiology has been defined as the study of the distribution of a disease in human populations and of the factors that influence this distribution. It applies to populations, not to individuals. The foundations of epidemiology date back to the nineteenth century when a few classic studies made a major contribution to the saving of life, particularly in respect of infectious diseases. One of the first epidemiological papers was published in 1849 by Snow, in which he pointed to contaminated water as the likely cause of a cholera epidemic in London. This was subsequently confirmed by other tests.

3.1 Types of data used in epidemiological studies

Most epidemiological studies from Snow's time onwards have been based on mortality data (i.e. information obtained from death certificates on the cause of death). In England and Wales these have been collected since 1839 and an annual publication of death statistics is produced. Although mortality data is now collected throughout the world it is important to consider the inherent limitations in such data. The inaccuracy of death certificates is such a limitation.

Barker (1984), said:-

"Epidemiological findings based on mortality are viewed with suspicion by many doctors. This is right, for the death certificate is primarily a legal document, not a record for medical research, and the accuracy of the diagnostic data is unknown. Furthermore, for most diseases mortality is an imperfect indicator of incidence."

'Cause of death' as indicated in the certificate is rarely confirmed by carrying out an autopsy on the body. In England and Wales only 9.2% of deaths were autopsied in 1928 rising to 28.4% in 1980; in Scotland the figure was only 15% (Roe, 1984). Elsewhere the figures vary from very low (developing countries) to 62.6% (Malmo, Sweden 1958-1969, Berge and Toremalm (1975)) and 64% (University Hospitals in Cleveland 1948-1973, Cechner et al (1980)). An insidious type of error in death certificates has been identified by Feinstein and Wells (1974): detection bias. In this

case the physician "is more likely to diagnose lung cancer in smokers than in non-smokers and in heavy than in light smokers". MacFarlane et al (1984) present evidence that many cases of lung cancer go undetected during life. They would therefore not be recorded on death certificates. No data are presented in this study as to whether or not the undetected cases were more, or less, likely to be smokers. Shortcomings in mortality data are further discussed in the following papers: Heasman and Lipworth (1966), Waldron and Vickerstaff (1977), Mori and Sakai (1984) and Mackenbach et al (1984). The joint report of the Royal College of Physicians and Royal College of Pathologists (1982) discusses this question in more detail. Changing criteria for diagnosing certain diseases may also be a problem (Watanabe et al 1987; Peto 1986).

An alternative approach is to use morbidity data (incidence of illness rather than death from illness), of which there are a number of sources of information such as cancer registries and general surveys (e.g. General Household Survey in the United Kingdom). One serious disadvantage of morbidity statistics is the fact that, at any particular point in time, not all persons suffering from a particular disease will have been diagnosed, or will even have contacted their doctor. For these and many other reasons most epidemiological studies are based on mortality data but even so the poor quality of the basic data, particularly older data, cannot be over-emphasised.

The end-point of most epidemiological studies is a figure called a relative risk ratio. This figure is intended to express the increase in risk of developing a specific disease if a particular factor is present in a population (eg smoking) compared to a population in which that factor is not present. So, in the case of smoking and lung cancer, if a study claims to have shown that smokers have a relative risk of 10 for developing lung cancer, then this means that in the study concerned it is claimed that smokers were 10 times more likely to develop lung cancer than non-smokers.

3.2 Types of epidemiological study

There are two broad approaches to the collection of epidemiological data (using mortality data) that are relevant to the study of the so-called smoking-associated diseases:

(a) the prospective method. A population (commonly called a cohort) is identified and the occurrence of, or pattern of, various factors which are thought to be related to disease are measured as accurately as possible (e.g. diet, cigarette smoking, exposure to environmental chemicals etc.). Measurement continues until the death of the subjects. Possible relationships between these measures and death from given diseases are examined after the subjects have died.

(b) the retrospective method. A population is identified that has been diagnosed to have or has already died from a given disease and deaths are related to relatives' recollections of the presence of factors thought to be relevant in causing that disease. A 'case-control study' is one type of retrospective study that starts with the identification of persons with the disease, who are then compared to a reference group without the disease; the relevant factors are then studied.

The first method is generally preferred because the data are considerably more accurate and objective. The difficulty in obtaining accurate recollections from relatives is obvious, and objective measurements are lacking.

There are various other options in the way in which epidemiological data can be analysed; the data for the population in question can be used as they stand (i.e. based on deaths in a given year in all age groups) or data for generations ('cohorts') born over successive periods of time can be used and compared: the latter approach is known as 'cohort analysis' and is discussed in Chapter 4 of this review.

3.3 Problems in epidemiological studies

(i) Precision

Random error may occur in all epidemiological studies. A major source of imprecision is the lack of knowledge about all of the risk factors that may be operating in a given disease. For example, a study measuring the effects of smoking, identified as one potential risk factor for lung cancer, in all probability will not measure an exhaustive list of all other potential risk factors for lung cancer. The estimate achieved for the association between smoking and lung cancer will, therefore, be imprecise because there is no way of knowing that a smoker who died of lung cancer was not exposed to other risk factors. Insufficiently large sample sizes and an imbalance in size between the control group and the study group can also lead to an imprecise result.

(ii) Validity

Systematic error or bias (as opposed to random error), can invalidate a study. There are three major types of bias: selection bias, information bias and confounding.

Selection bias is any bias arising from the procedure by which the study subjects were chosen from the population as a whole. For example, if for some reason smokers suffering from disease are more amenable to participating in a study than non-smokers with the same disease, then the results of the study would be biased because they would give an overly large estimate of the size of the association between smoking and the disease.

Information bias involves misclassification of the study subjects with respect to the disease or to their exposure characteristics (e.g. incorrect information being recorded about smoking status, duration of smoking, number smoked etc).

Confounding occurs when the control group and study group are not strictly comparable due to inherent differences in background disease: usually due to exposure to other risk factors. For example, if a control group of non-smokers in a lung cancer study contained a high proportion of diesel bus garage workers who are also believed to have a high risk of lung cancer, whereas the smoking group did not include such people, then the study would be invalid because the 'background' rate of lung cancer in the two populations would be different. Other potential common confounders include age and social class.

3.4 Use of data from epidemiological studies: causality

It is important in any scientific study, once a result has been obtained, to see whether or not the result is statistically significant i.e. whether or not the observed results could have been observed by chance. In epidemiological studies, this is particularly important when the relative risk is a low one.

An epidemiological study may reveal a statistically significant association between a disease and a particular factor. The question then remains as to whether any association that is found is best explained by the hypothesis that the factor caused the disease or by some alternative hypothesis.

This is discussed in "A Dictionary of Epidemiology", J M Last, ED., (1983), in terms of putting together a set of 'criteria for causality' i.e. if an association passes all the stated criteria it will more likely be considered by epidemiologists to be a causal one. The following criteria were proposed by Bradford-Hill, and are similar to those proposed by the US Surgeon-General in 1982.

1. Consistency - The association is consistent if the results are replicated when studied in different settings and by different methods. (eg Are smokers in all studies and all populations more likely to develop lung cancer than non smokers?)

2. Strength - This is an expression of the disparity between the frequency with which a factor (eg smoking) is found in the disease (eg lung cancer) and the frequency with which it occurs in the absence of the disease. Not to be confused with statistical significance. (eg Do non-smokers develop lung cancer?).

3. Specificity - This is established with the limitation of the association to a single putative cause and single effect. (ie If a disease is associated with many different factors it is difficult to ascertain that any one of them is causal).

4. Dose-response relationship - This is established when an increased risk or severity in disease occurs with an increased quantity ("dose") or duration of exposure to a factor. (eg Do heavy smokers develop more lung cancer?)

5. Temporality - The exposure to a putative cause always precedes, never follows, the outcome. (eg In the case of smoking, smoking should have begun well before the time at which lung cancer was believed to begin developing - on average 20 years before the disease is diagnosed).

6. Biological plausibility - It is desirable that the association agree with current understanding of the response of cells, tissues, organs, and systems to stimuli. This criterion should not be applied rigidly. The association may be new to science or medicine. As Sherlock Holmes advised Dr. Watson, "When you have eliminated the impossible, whatever remains, however improbable, must be the truth." (eg Is there a known mechanism by which smoking could potentially activate a step in the development of cancer or other diseases?)

7. Coherence - The associations should not conflict with the generally known facts of the natural history and biology of disease.

8. Experiment - It is sometimes possible to appeal to experimental, or quasi-experimental evidence, e.g., an observed association leads to some preventive action. Does this action in fact prevent?" (eg If people stop smoking, does their risk of lung cancer diminish?)

It has been stated that one can explain an association between a given factor (e.g. smoking) and a disease in terms of one or more of the following:-

1. The factor causes the disease.
2. The disease causes the factor.
3. Another factor causes both the disease and the original factor.

Consideration of the above criteria is used to assess which of the above is the most likely explanation. The epidemiological criteria (nos 1-5) will be used as the basis for discussion in the following chapter.

4. SMOKING-ASSOCIATED DISEASES

4.1 Lung Cancer

Lung cancer was a disease that was first observed among miners; for example the incidence of lung cancer in a group of miners in Czechoslovakia during the period 1875-1912 was estimated to be about 54 times greater than expected (Archer and Lundin (1967)). Attention was focussed on radioactive emissions from radium as a possible cause of this excess rate of lung cancer early this centrury.

As noted earlier a possible association between cigarette smoking and lung cancer was first suggested by Adler (1912) and since the 1950's many epidemiological studies have claimed an association between smoking and lung cancer. As noted in the Introduction, many doctors have made the judgement, based on these studies, that there is a causal relationship between smoking and lung cancer.

In addition to mining and smoking, many other factors have been claimed to be associated with lung cancer. Papers describing anomalies in the association between smoking and lung cancer are considered first in this review; papers alleging associations between lung cancer and other factors follow. Because of their large numbers, papers related to lung cancer are considered in relation to the criteria proposed by Bradford Hill for making judgements on possible causal relationships between factors and diseases.

(i) Consistency

"The association is consistent if the results are replicated when studied in different settings and by different methods".

Relative risk ratios for 35 retrospective studies have been published (Report of the U.S. Surgeon General's Report, 1982). These studies cover the period 1939-1970: for males the ratios range from 1.2 to 36.0, for females from 0.2 to 5.3. This wide range has been commented on by Burch (1383) as follows:

"With ratios showing a range overall, of more than two orders of magnitude it is not self-evident that any acceptable criterion of consistency has been satisfied. The Committee would appear to have been faced with the choice of either abandoning the causal interpretation, or of explaining away this enormous diversity. Instead, we are told (p.34): "Regardless of the method, these studies have consistently found an association between smoking and lung cancer". The fact that Table 4 gives two examples of relative risk ratios less than unity (they are negative associations) has either been overlooked, or negative and positive associations are both subsumed under 'associations'. Might I suggest that ratios with, say, 95% confidence limits based on the numbers of deaths and age-standardization would assist evaluation and, when particular findings differ by some arbitrary degree from the overall weighted mean, comment would be appropriate? On a simple reading of Tables 4 and 5 any plausible criterion of consistency would appear to be overwhelmingly violated."

Geographical and ethnic differences in lung cancer risk can also be used to argue against consistency in that similar results are not obtained in all populations studied. For example, Hinds et al (1984) found widely varying relative risks for lung cancer associated with smoking in various ethnic groups of women in Hawaii. The author claims that, among Chinese and Japanese women in Hawaii, only a small number of cases were associated with smoking compared to a larger number of cases in Hawaiian women. It is suggested that there are other factors influencing lung cancer risk in Chinese and Japanese women.

A paper by Roe and Walters (1965) discusses high lung cancer rates in British immigrants in other parts of the world in terms of a "British Factor".

Sex differences are also of relevance here; Burch (1978) discussed the fact that women smokers in many studies have been alleged to have lower relative risks for developing lung cancer, regardless of smoking habits.

(ii) Strength of Association

This is an expression of the disparity between the frequency with which a factor is found in association with the disease and the frequency with which it occurs in the absence of the disease. The incidence of lung cancer in non-smokers is therefore of relevance here.

Koo et al (1983) found that female non-smokers had about the same relative risk for lung cancer as did smokers smoking for less than 14 pack-years. ('Passive Smoking' did not account for this.) Kung et al (1984) suggested that factors other than cigarette smoking may be responsible for the "peculiar and changing historical pattern" and the female predominance of lung cancer in Hong Kong Chinese.

Some studies have suggested that the rate of lung cancer is rising in non-smokers against a background of decline, or no change, in lung cancer rates in smokers, and have suggested reasons why this might be so. For example, a number of papers are appearing in the scientific literature that suggest that the relative incidence of different types of lung cancer is changing. Squamous cell carcinoma, which is more common in smokers than non-smokers, has been declining in some countries relative to adenocarcinoma, which is more common in non-smokers. A number of authors have therefore suggested that, in countries where adenocarcinoma is increasing, non-smoker deaths from lung cancer (rather than smoker deaths) are increasing.

Hanai et al (1987) found that adenocarcinoma of the lung appeared to be three times more frequent in Osaka, Japan than North-West England, and also that many Chinese and Japanese women with lung adenocarcinoma (77% in Osaka) did not smoke. Anton-Culver et al (1988) noted that adenocarcinoma in the USA (occuring primarily in female non-smokers) was catching up with the incidence of squamous cell carcinoma (occurring primarily in smokers), and suggested that "Differences in cell type which persist after adjusting for smoking suggest that different etiologic factors are responsible". Gazdar et al (1988), also in the USA, agreed that adenocarcinoma, "the commonest type of lung cancer occurring in women, young patients and nonsmokers", was increasing, and Reyes et al (1987) came to similar conclusions. Watanabe et al (1987) in Japan noted that adenocarcinoma had increased rapidly from 1966 to 1985 in females, whereas squamous cell carcinoma had decreased.

A number of factors have been proposed as alternatives to the smoking hypothesis (see also next section, iii). Wynder and Covey (1987) suggest that endogenous (internal) factors (diet, hormones) may be of particular importance in the development of adenocarcinoma, and suggest that the dominance of the hypothesis of cigarette smoking as a risk factor has led to the relative neglect of other factors.

(iii) Specificity

Some of the papers which show an association between lung cancer and factors other than smoking are now discussed. It should be remembered that the criterion for specificity is:- "This is established with the limitation of the association to a single putative cause and single effect."

RADON

Radon is a radioactive gas that seeps out of granite rock and that has been found in high concentrations in houses and buildings built on this kind of rock. In 1986 the US Environmental Agency reported that 1 in 8 American homes harbour dangerous amounts of radon. Radon has been associated with lung cancer in a large number of studies (e.g. Axelson, 1984; Archer 1987).

DIESEL

A number of studies have suggested that inhalation of diesel or petrol fumes is associated with lung cancer (e.g. Blumer & Reich, 1980; Garshick et al, 1987; Gustafsson et al, 1986).

OCCUPATION

Lung cancer has been associated with the following occupations:- mining (Axelson, 1983; Bertrand et al, 1987); foundry work (Palmer & Scott, 1981); welding (Beaumont & Weiss, 1981); shipbuilding construction and lumber work (Blot et al, 1982); painting (Dalager et al, 1980); tin mining (Sun, 1987); sugar cane farming (Rothschild & Mulvey, 1982); cotton working (Levin et al, 1987) and the pulp and paper industry (Jappinen & Tola, 1986). Schoenberg et al (1987) also found elevated risk of lung cancer in

27 categories of employment, including masons and tile-setters, janitors and cleaners, printing workers, trucking service, warehousing and storage workers, shipbuilders, welders, burners, sheet metal workers and boilermakers. In the wood industry in Finland, Kauppinen et al (1986) found elevated risks of lung cancer associated with exposure to wood dust, pesticides, phenol, terpenes and other products of heating coniferous woods. Blot (1984) classifies the following as "known occupational lung carcinogens": arsenic (National Academy of Sciences, 1977); asbestos (Doll, 1955); bischloromethyl ether (IARC, 1982; Mahler & De Fonso, 1987); chromium compounds (Machle & Gregorius, 1948); mustard gas (IARC, 1982); nickel-refining processes (IARC, 1982; Doll, 1958); polycyclic aromatic hydrocarbons e.g. in the coal carbonisation process (Lloyd, 1970; IARC, 1982). Blot also considers the following to be suspected occupational lung carcinogens: acrylonitrile, used in the production of plastics, fibres and synthetic rubber (IARC, 1982; Delzell & Monson, 1981), beryllium (Wagoner et al, 1980) and vinyl chloride (Waxweiller et al, 1981). Sulphuric acid has also been suggested to increase lung cancer mortality (Beaumont et al, 1987). One of the more interesting occupational links is the suggestion that butchers are particularly prone to lung cancer (Lynge et al, 1983).

Sterling (1978) argues that many diseases associated with smoking actually may be of occupational origin and that smoking has been used to divert attention away from occupational and environmental hazards. Simonata et al (1988) note that in some populations, occupation can account for up to 40% of lung cancers.

ENVIRONMENT

Shy (1984) suggests that there are three lines of epidemiological evidence that suggest an association between air pollution and lung cancer: firstly that there is an increased risk for lung cancer in urban areas that is not explained by differences in smoking habits; secondly that carcinogens (eg soot, tars, benzo(a)pyrene and other combustion products) are found in ambient air; and thirdly that cross-sectional geographical studies suggest a relationship between atmospheric pollution and lung cancer. Papers by Haenszel & Taeuber (1964) and Muir & Staszewski (1986)

support these suggestions. Johnson (1985) lists 99 chemicals for which recommended ambient air quality guidelines exist in the USA. A number of studies have identified particles in the lungs both of smokers and non-smokers, the source of which is assumed to be urban air. Churg & Wiggs (1987) found a wide variety of mineral particles in the lungs of urban cigarette smokers and found that 80% of the particles were assumed to come from urban air (talc, kaolinite, micas, feldspars, crystalline silica). Paoletti et al (1987), in a study of inorganic particulate matter in the lungs of 10 urban subjects, found 17 different mineral types and 16 metal elements to be present. Some of these particles from urban air have been suggested to be carcinogenic for example, Sasaki et al (1987) found an organic extract of airborne particles to be carcinogenic in mice.

With reference to the home environment and indoor air quality, Leung (1977) suggested that the high incidence of lung cancer in women in Hong Kong is associated with use of the kerosene stove. Gao et al (1987) found that exposure to cooking oil vapours, particularly rape seed oil, similarly was associated with a high risk of lung cancer in Chinese women.

DIET

A small amount of evidence exists to suggest that diet may be a factor in lung cancer. Wynder et al (1987) found that intake of calories from dietary fat was highly significantly associated with lung cancer mortality. Hinds et al (1983) found a dose-response relationship between dietary cholesterol and lung cancer in men but not in women. Koo (1988) found that consumption of certain types of food eg leafy green vegetables, carrots, tofu, fresh fruit and fresh fish was associtated with a decreased risk of lung cancer in Hong Kong Chinese women who never smoked. The relationship between diet and disease in general is discussed in chapter 6.

ALCOHOL

Hinds et al (1980), Potter & McMichael (1984) and Pollack et al (1984) have suggested that alcohol is a risk factor for lung cancer.

PERSONALITY/STRESS

Linn & Stein (1987) suggest that there are certain personality characteristics that can identify lung cancer patients. Persky et al (1987) found that depressed individuals had a higher risk for incidence of

cancer in general, and Manz (1987) suggested that work-dependent stress plays a large role in tumour development. Interestingly, Mangan and Golding (1984) suggested that for mortality in general, amongst individuals leading stressful lives, smokers have lower mortality ratios than non-smokers. Grossarth-Maticek et al (1984) suggested that persons reporting 'hopelessness' as a characteristic showed an increasing risk ratio for the development of cancer. A gradual increase of cancer became evident more than 3 years after an event causing unresolved depression and hopelessness of more than 1 year's duration.

FAMILIAL/GENETIC FACTORS

Miyamoto et al (1987) suggest that there are familial factors in serum selenium and vitamin E levels among families of lung cancer patients (ie there are lower levels in lung cancer families) that may reflect a genetic predisposition to the development of lung cancer. (These vitamins have been proposed to exert a protective effect against cancer, see Chapter 6.) Tokuhata & Lilienfield (1963), Kramer et al (1987), Jones (1977) and Ooi et al (1981) suggest that lung cancer clusters in families, and that the clustering is not explained by familial tendencies to smoke. Similarly, Sellers et al (1987) and Goffman et al (1982) suggest that some types of cancer may cluster in families of lung cancer patients and believes that this supports the hypothesis of genetic susceptibility.

DRUGS

Friedman (1983) discusses an association between use of barbiturates, benzodiazepines (eg valium) and lung cancer.

GEOGRAPHICAL and ETHNIC FACTORS

Because of their large role in disease in general these factors are considered separately in Chapter 5.

MISCELLANEOUS

Holst et al (1988) reported that keeping of pet birds in the home was significantly associated with the development of lung cancer, independently of the smoking habits of the owner. The relative risk ratio was 6.7. Selby and Friedman (1988) reported that a lower risk of several types of cancer, particularly lung cancer, was observed in women who had depleted stores of iron in their body.

(iv) Dose-Response Relationships

In the absence of any other confounding elements a causal relationship between a factor A and a disease B should also result in a sensible dose-response curve (for example, increasing rates of lung cancer as smoking increases) in any population studied. It has been suggested in many studies investigating the association between smoking and lung cancer that such a dose-response relationship occurs; however, anomalies in the dose-response relationship have been discussed by Burch (1984).

(v) Temporal Relationship

The temporal relationship between a disease and its putative cause can be conveniently studied by a relatively new statistical technique called cohort analysis (analysis of disease incidence in successive generations). Disease incidence (eg lung cancer) in different generations is compared with the presence of selected environmental factors (eg smoking) in those generations.

Early papers looking in a very simple way at incidence of smoking-associated diseases in successive generations pointed out that the patterns of incidence of such diseases did not always correlate strongly with patterns of smoking. Todd et al (1976) concluded that the peak incidence of the so-called smoking-associated diseases preceded peak cigarette consumption. The maximum rate of these diseases occurred in those generations whose incidence of smoking was lower than that of later generations. Belcher (1987) arrives at a similar conclusion and particularly points out as an anomaly a low incidence of lung cancer in the group of women who had smoked more than any other in the history of the UK.

In the UK, a considerably more sophisticated approach to cohort analysis appeared in 1982. Death rates for a given disease are regarded as being related to three factors: an age value (showing whether or not the disease increases with age), a period of birth (or generation) value (showing what happens to disease rates over different generations) and a period of death value (giving a control for changes in diagnosis or treatment of the disease). The main factor of interest is of course the generation or 'cohort' value; the other two factors provide controls by

which one can be sure that an observed generation effect is a real effect and not, for example, an increase in a disease over time because diagnosis has become easier, or a decline because treatment has become easier. A brief introduction to this form of analysis is given by Osmond, et al (1982).

Analyses by Osmond et al (1982, 1983) suggest that cancer rates in general have been declining for some time, not increasing as is generally believed. These results (e.g. for lung cancer) can be compared to the cigarette consumption figures produced by Todd et al (1976) on a constant tar basis. For lung cancer and smoking, the results of these sophisticated analyses essentially confirm the results of the earlier work described at the beginning of the section. For women it can be noted that there is no evidence of a decrease in cigarette consumption (on a constant tar basis) for any age group*, yet, according to Osmond and colleagues, lung cancer has fallen on a generation-by-generation basis by about the same amount as it has in men, but over a different period of time. For men the maximum lung cancer rate occurs for the cohort born around 1900 and then begins to decline. This is not the maximum for cigarette consumption which, according to Todd's figures, reached a maximum for the generation born around 1920. Further, since the calculations made by Todd et al on a constant tar basis assume no "compensation"** by smokers, they may, therefore, underestimate actual tar levels. For women, the peak lung cancer rate is reached in the cohort born around 1925.

Lee et al (submitted for publication) also consider cohort analysis of lung cancer rates compared to cigarette consumption and discuss what they consider to be a particularly striking anomaly i.e. the failure of cigarette consumption trend data to predict trends in lung cancer rates in the youngest age groups. This anomaly, they report, is evident in both sexes but is particularly clear in females. The authors therefore suggest that there is some factor other than smoking that was responsible for most of the lung cancers occurring in women in the early 1940's.

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* Single exception age 40-44, 2% decrease, 1931 cohort v 1926 cohort

** Compensation is the tendency to equalize tar intake from cigarettes with different tar deliveries, by taking for example larger or more frequent puffs.

Burch (1988) carried out a cohort analysis of overall mortality in successive generations and correlated it with cigarette consumption in these generations. He, similarly, found no significant correlation between the two factors.

Osmond and Gardner's method of analysis has also been carried out by Lee et al (submitted for publication) in the following countries and compared to cigarette consumption in those countries: Australia, Austria, Canada, Denmark, England and Wales*, Finland, France, Japan, Netherlands, Northern Ireland, Norway, Scotland, Sweden and West Germany. For Canada these graphs can be compared with detailed cigarette consumption data (available for Canada on a generation basis but without correction on a constant tar basis) (Todd (1979)).

In Canada, for lung cancer, the incidence by generation is greatest for men and women born around 1930 and then declines. Yet Todd's data suggest that there is little if any evidence of any subsequent reduction in cigarette consumption for men, at least up to the generation born in 1961. For women, all the evidence points to an increase in consumption up to and including the generation born in 1961. In contrast to the graphs for the UK, the Canadian results show trends in period values, suggesting that changes in diagnoses are occurring. (Osmond et al (1983) comment that "Changes in diagnosis, classification and treatment are likely to show period changes").

Levi et al (1987) carried out cohort analysis on a number of cancers in Switzerland. For lung cancer in men, peak incidence was for generations born in 1910 and, again, a moderate decline was observed in more recent cohorts. For females, however, upward trends were observed up until generations born in 1945. These data have not yet been correlated with cigarette consumption in Switzerland.

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* For comparison (where possible) with Osmond and Gardner's calculations, analyses were also carried out by Lee for England and Wales. Osmond and Gardner graphs were replicated in all cases when comparison was possible with Lee's results.

4.2 Other Cancers

The Report of the US Surgeon-General (1982) suggests a number of cancers other than lung cancer that have been claimed to be associated with smoking; however, the estimated percentages of these cancers that he attributes to smoking are considerably lower (larynx and oral cavity cancer: 50-70%; oesophageal cancer: 50%; bladder cancer: 30-40%; pancreatic cancer: 30%). However, in spite of these attributions, problems with the associations are noted in the Report. For example, the Surgeon General states, for bladder cancer, that "several of these studies also show a moderate dose-response relationship; however, this relationship is not as strong as that noted between smoking and lung, laryngeal, oral and oesophageal cancers. Comparisons of mortality ratios for selected causes of disease suggest that the specificity of the association is not as great as that noted for the above cancers".

For kidney cancer, he notes: "The strength of the association of cigarette smoke related to kidney cancer risk is less marked than that for cancer of the other sites discussed above. Chemical elements such as lead and cadmium, hormones, ionising radiation, genetic susceptibilities, as well as tobacco smoke have each been suggested as potential etiologic (causal) factors in this disease."

It is also accepted by the Surgeon General that the evidence for a causal association between smoking and pancreatic and stomach cancers is inadequate. In the case of cervical cancer, which has in a small number of studies been claimed to be associated with smoking, the Surgeon-General states: "There are conflicting results in studies published to date on the existence of a relationship between smoking and cervical cancer; further research is necessary to define whether an association exists and, if so, whether that association is direct or indirect."

The major 'other cancers' for which the Surgeon-General assumed that smoking was the major cause and that the association was a causal one were, therefore, laryngeal, oral and oesophageal cancers.

(i) Laryngeal, oral and oesophageal cancers

Osmond and colleagues (1983) examined the more common forms of cancer in the UK by their method of cohort analysis, and their results for cancers of the larynx and oesophagus show a wide variation in the time trends for the cohort values (pattern of disease over different generations).

Burch (1984) explored the basis for the association between cigarette smoking and oesophageal cancer. He reported that temporal trends in England and Wales from 1911 to 1980 showed that death rates from oesophageal cancer do not correlate positively with rates of cigarette smoking. Cohort analysis has also been carried out by Lee (unpublished data, 1985) for laryngeal and oesophageal cancer in other countries.

A study by de Stefani and Carzoglio (1985) indicates that laryngeal cancer in Uruguay is falling for younger generations against a pattern of increasing cigarette sales. Wey et al (1987) found a high percentage of women non-users of tobacco and alcohol who had oral cancer which was therefore assumed to be associated with other risk factors.

Burch (1984) also suggested that genetic predisposition may play a role in oesophageal cancer.

(ii) Bladder Cancer

For bladder cancer, occupation has also been claimed to constitute a risk (Brownson et al, 1987), as have artificial sweetners (Miller, 1977). Hoar and Hoover (1985) found that truck drivers had a high rate of bladder cancer.

(iii) Cervical Cancer

For cervical cancer, age at first sexual intercourse and number of sexual partners are acknowledged to be major risk factors, as is the presence of human papilloma virus (See Surgeon-General, 1982). A number of scientists have noted that the association between cervical cancer and smoking which, although very small, has been observed in a number of studies, is in fact due to a confounding variable: sexual activity. For example, La Vecchia et al (1986) found that 41% of those who had more than one sexual partner were smokers, compared to only 22% of those with none or one only.

(iv) Other Cancers

It is also worthy of note that there are a number of studies reporting negative associations between smoking and some cancers, which would be interpreted by some as a protective effect. Stockwell and Lyman (1987), Lawrence et al (1987), Franks et al (1987) and Levi et al (1987) all

report results of studies suggesting that female smokers have a significantly lower relative risk of developing endometrial cancer (cancer of the walls of the uterus) than do non-smokers. O'Connell et al (1987), in a study reporting an elevated risk of breast cancer in women who consume regular amounts of alcohol, also reported a reduced risk of breast cancer in smokers compared to non-smokers. Yen et al (1987) reported that the use of cigarettes was associated with decreased risk of extrahepatic bile duct cancer.

4.3. Diseases of the Heart and Blood Vessels

Considerable discussion has continued on the possible role of smoking in coronary heart disease. Both sides of the argument have been well documented in recent reviews, 'The Health Consequences of Smoking, Cardiovascular Disease, a report of the U.S. Surgeon General' (1983) and 'Cigarette Smoking and Heart Disease,' Tobacco Institute (1983).

Smoking has been implicated as a risk factor primarily in atherosclerosis, which underlies many types of cardiovascular disease. However, smoking has not been associated with all cardiovascular diseases. In the case of the hypertension (elevated blood pressure), in fact, smokers have been suggested to develop this less frequently than non-smokers, as they have consistently been found to have lower baseline blood pressure than non-smokers (e.g. Green et al, 1986). Although many epidemiological studies have claimed to observe an association between smoking and cardiovascular disease, several studies have failed to do so. For example Lapidus et al (1986) found no significant increased risk for women smokers for myocardial infarction, angina pectoris, electrocardiographic changes suggesting ischaemic heart disease, stroke or death from all causes. Menotti et al (1987) found that smoking (along with blood pressure and serum cholesterol) was associated only with cases ending up as sudden deaths and not with myocardial infarction (without sudden death) or chronic coronary heart disease.

Burch (1980) put forward the hypothesis that heart disease arises in the population as a result of spontaneous mutations or changes in cells, rather than simply as a response to the presence of certain risk factors.

Other factors in cardiovascular disease

Many studies have suggested that smoking is only one of many possible risk factors for cardiovascular disease. Hopkins and Williams (1981) surveyed no less than 245 suggested coronary risk factors. Paffenbarger and Hyde (1986) suggest a number of additional factors; they attribute 21% - 25% risk to cigarette smoking and the rest to hypertension, sedentary lifestyle, overweight, and history of parental cardiovascular disease. High blood pressure, for which smokers seem to have a lower risk than non-smokers, was identified as a major predictor of atherosclerosis in a recent study (Reed et al, 1987) and as a predictor of coronary heart disease in general by Kannel (1987). A variety of other factors have been implicated in cardiovascular disease. Systematic comparisons of populations show large differences in the incidence of coronary heart disease (Shaper and Pocock, 1987; Keys, 1970). Keys also suggested that risk factors for coronary heart disease have differing relevance in different areas. Studies of migrants show that their risk factors and disease incidence soon approach the levels of the adopted culture (Marmot et al, 1975). Kangan et al (1974) came to similar conclusions, believing that both 'genetic' or 'ethnic' and 'environmental' factors are important.

A great deal of emphasis has been placed on dietary contributions to heart disease; in particular, high dietary cholesterol (Reed et al, 1987; Shekelle et al 1981; Kushi et al, 1985.) Alcohol has been pointed out as another risk factor (Dyer et al, 1981); as have dietary salt (Gleibermann, 1973), obesity (Hubert et al, 1983), sociological indices, social mobility, anxiety and neuroticism, life problems, stress (Jenkins, 1976; Marmot, 1983), oral contraceptives, and removal of the ovaries in menopause (Colditz et al, 1987).

Whilst it is frequently stated by medical authorities that heart disease is increasing in many countries, Stehbens (1987) questions whether this is really the case, criticising the sources of the other data. Leeder et al (1984) also present evidence that heart disease may be declining, and Ragland et al (1988) suggested that heart disease among men in the USA has been declining since 1960-1965.

Cohort Analysis Applied to Ischaemic Heart Disease (IHD)

In the previous sections of this chapter cohort analysis has been applied to various forms of cancer. Mortality figures for heart disease can also be examined by the same form of analysis.

As with lung cancer data, the trends in IHD can be compared with trends in cigarette consumption when these are known in any detail, i.e. for England and Wales and for Canada. There are a number of other countries where generation values for incidence of IHD are approximately constant (or decreasing) against a background of generally increasing cigarette consumption. This comparison speaks for itself. In addition, in some countries there is a downward trend in IHD incidence which may be contrasted with the trends noted for lung cancer in these countries, which are sometimes in the opposite direction. If both diseases were causally related to smoking, one would expect their patterns to be similar to each other.

4.4 Chronic Obstructive Lung Disease

Chronic obstructive lung disease has been reviewed at length in 'The Health Consequences of Smoking: Chronic Obstructive Lung Disease', Report of the US Surgeon General, (1984) and in 'Cigarette Smoking and Chronic Obstructive Lung Diseases: The Major Gaps in Knowledge', The Tobacco Institute (1984). Consequently only a brief description follows.

The disease, referred to by the abbreviation COLD, comprises three separate, but often interconnected, disease processes:

(1) chronic mucus hypersecretion, resulting in chronic cough and phlegm production (in broad terms what was known as bronchitis)

(2) airway thickening and narrowing with expiratory airflow obstruction and

(3) emphysema, which is the presence of abnormal airspaces within the lung.

Whilst it would be preferable to consider these diseases separately they are so frequently confused with each other that there is considerable uncertainty about which of the above processes are referred to by the terminology used in any but the most recent studies.

A large number of studies have pointed to factors other than smoking that are associated with COLD. There are gross differences in bronchitis, emphysema and asthma by social class (see Burr & Holiday, 1987). Bakke et al (1987) point out that many non-smokers in Norway suffer from respiratory symptoms.

Occupation also plays a major role in COLD, as illustrated by the study of Becklake et al (1987) in South African gold miners and Nemery et al (1987) in coal-miners. Prediletto et al (1987) found that in North Italy certain occupations were predictive of respiratory disease, and Korn et al (1987) found that occupational exposure to dust, gas or fumes was a risk factor for respiratory disease in the USA. Schwartz and Baker (1988) found that painters were at risk for developing air flow obstruction. Sterling (1984) raised the possibility that smoking may actually exhibit a certain preventative effect in some occupational exposures.

Environmental exposures and air pollution have also been raised as important risk factors. Euler et al (1987) reported that exposure to sulphur dioxide and total suspended particulates in the atmosphere was associated with COLD in 7th-Day Adventists. Gamble et al (1987) found respiratory symptoms in diesel bus garage workers as did Garshick et al (1987) in railroad workers exposed to diesel fumes.

It has been suggested that smoking contributes to asthma and bronchitis in adolescence; however, Oechsli et al (1987) found that age of onset of asthma preceded smoking in 90% of subjects and concluded that the two were not causally related.

Reid et al (1983) found that breathing high oxygen concentrations can cause lung injury, which is of particular interest since increased oxygen levels are often used in the treatment of chronic lung disease.

Interestingly, in spite of the continued emphasis on the problem of COLD, Peach (1986) suggested that for ages 45 - over 75, chronic bronchitis and emphysema have been declining in England and Wales since around 1963.

Genetic factors have also been implicated in some cases of COLD (see Chapter 7); it has been suggested that COLD tends to cluster in families (Cohen and Chase, 1978).

Lee et al (submitted for publication) carried out cohort analyses of data on chronic obstructive pulmonary disease and emphysema in relation to trends in cigarette smoking. A similar cohort pattern to that for lung cancer was observed i.e. a peak in incidence of disease in the early part of the century followed by a decline in disease rates. The decline in rates for COPD was observable in generations born from 1863 onwards. It is suggested that the factors responsible may be related to social class, differences in living conditions, or differences in childhood respiratory infection.